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REVIEW

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Motion Sickness: Current Knowledge and Recent Advance

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SUMMARY

Motion sickness (MS) is a common physiological response to real or virtual motion. Numerous studies have investigated the neurobiological mechanism and the control measures of MS. This review summarizes the current knowledge about pathogenesis and pathophysiology, prediction, evaluation, and countermeasures of MS. The sensory conflict hypothesis is the most widely accepted theory for MS. Both the hippocampus and vestibular cortex might play a role in forming internal model. The pathophysiology focuses on the visceral afference, thermoregulation and MS-related neuroendocrine. Single-nucleotide polymorphisms (SNPs) in some genes and epigenetic modulation might contribute to MS susceptibility and habituation. Questionnaires, heart rate variability (HRV) and electrogastrogram (EGG) are useful for diagnosing and evaluating MS. We also list MS medications to guide clinical practice. Repeated real motion exposure and combined visual-vestibular interaction training accelerate the progress of habituation. Behavioral and dietary countermeasures, as well as physiotherapy, are also effective in alleviating MS symptoms.

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Introduction

Motion sickness (MS) is a feeling of unwellness caused by motion, especially during traveling and virtual reality immersion. The main symptoms of MS include autonomic reactions (nausea, vomiting, pallor, sweating, hypersalivation, and stomach awareness) and sopite syndrome referring to drowsiness, lethargy, and persistent fatigue [1]. Intact vestibular apparatus and sufficient provocative stimulation are prerequisites for MS. There are great individual differences in MS susceptibility, which is thought to be a result of gene-environment interaction [2]. Although the etiology and precise neurobiological mechanism of MS are still ambiguous, several hypotheses have been proposed in which the sensory conflict hypothesis is the most widely accepted theory. Varieties of countermeasures have been developed and successfully used for decades.

Pathogenesis and Pathophysiology

Sensory Conflict Theory

The "sensory conflict and neural mismatch" theory was originally proposed by Reason and Brand. It is currently accepted for explaining MS [3]. MS will develop when mismatches happened between the integrated pattern of sensory information under real motion (e.g., in boats, cars, and airplanes) or virtual environment (e.g., watching 3D video films) and the anticipated "internal model" formed under normal or experienced conditions [4]. The physiological significance of "neural mismatch" is to initiate sensory-motor learning and promote self-adjustment, ultimately producing MS habituation under novel locomotion environment [5].

Recent studies have added new knowledge to sensory conflict theory. Cullen and his colleagues recently identified sensory conflict neurons in the VN and cerebellum. They found that "vestibular only" (VO) VN neurons and "unimodal" rostral fastigial nucleus (u-rFN) cerebellar neurons only reacted to passive head movement (exafferent) but not to anticipated active afference (reafference) in primates [6]. These sensory conflict neurons may receive inhibitory innervations canceling "reafference" that matches the experience in the "internal model." As the sensory conflict theory suggests that neural storage of the experienced motion pattern can produce novel "internal model," it can be presumed that the "exafference" might also be canceled by novel "internal model" established after habituation induced by prolonged or repeated passive motion exposure (Figure 1).

Several lines of evidence suggest that brain regions involved in space orientation and motion perception (hippocampus and vestibular cortex) are areas where internal model stores [7,8]. As for the hippocampus, forward–backward translocation and passive rotation can induce theta rhythm in dentate gyrus and CA1 regions while lesion in these regions can aggravate MS, suggesting

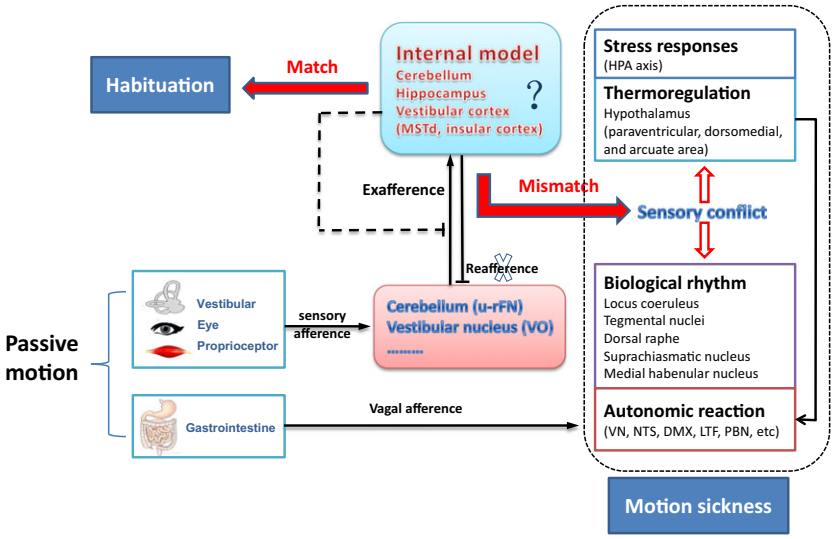

Figure 1 Sensory conflict theory and pathophysiological process of MS.

the hippocampal involvement in processing sensory conflict information [9–11]. In the vestibular cortex, electrophysiological experiments showed that bilateral labyrinthectomy significantly decreased the firing rate of neurons in dorsal part of middle superior temporal (MSTd) during physical rotation and translation in the dark, but not in the visual condition [12]. During large-field visual motion stimulation, inhibitory visual-vestibular interaction was observed in brain regions connected indirectly with MSTd in monkeys [13]. A recent fMRI study showed that long-term spaceflight significantly reduced intrinsic connectivity in insula cortex in a cosmonaut [14]. These lines of evidence supported that the vestibular cortex might play a role in visual-vestibular sensory conflict and possibly in forming "internal model."

Pathophysiological Mechanisms

Theoretically, activating sensory conflict neurons may trigger autonomic reaction through vestibulo-autonomic pathways that connect the VN complex with central autonomic regions [15,16]. Yates et al. have confirmed that vestibular system regulates cardiovascular function during movement and changes in posture via vestibulo-sympathetic reflex [17]. Although the contribution of sensory conflict neurons to VN-autonomic regulation is still ambiguous, downstream pathophysiological mechanisms of MS are updated by recent studies emphasizing visceral vestibular convergence, vestibulo-thermal regulation, and MS-related endocrine (Figure 1).

It has been demonstrated that brain regions associated with nausea and vomiting not only receive vestibular afference but also converge gastrointestinal (GI) signal [18], suggesting that visceral mechanosensory input might facilitate VN-autonomic reaction during MS. Ossenkopp et al. for the first time reported that MS can induce hypothermia which has recently been proved to be caused by increased heat loss resulting from peripheral vasodilatation [19,20]. Ngampramuan et al. proposed that the vestibular thermoregulatory symptoms may serve as a core pathophysiological element of motion-induced nausea in mammals [21]. As body temperature and biorhythms are significantly disrupted by chronic hypergravity and bilateral vestibular loss [22], we speculate that vestibular system might participate in keeping homeostasis during MS via connections with thermal and rhythmic regulation centers (Figure 1).

In addition to autonomic reactions, MS also accompanies stress hormones release and endocrine responses habituated over repeated motion exposure [23]. Nevertheless, temporal changes of blood hormones, such as arginine vasopressin (AVP) and adrenocorticotrophic hormone (ACTH), did not synchronize with those of motion-induced nausea, suggesting that activating hypothalamic–pituitary–adrenal axis might be a general stress response to provocative motion [24]. Recently, ghrelin, an endogenous ligand for the growth hormone secretogogue receptor, was observed to be related to acute nausea or vomiting [25]. In animals and humans, ghrelin was found to have gastro-prokinetic activity via facilitating gastric cholinergic activity [25]. Our study revealed that plasma ghrelin levels were positively correlated with severe seasickness-induced autonomic responses in humans (unpublished data), which suggests that gastroenteropancreatic hormones might play a role in MS development. Nevertheless, more detailed evidence is required to verify this hypothesis.

Genetic Contributions

MS is a conserved and a cross-species phenotype (from fishes, amphibia to mammals) with a heritability around 57–70% in humans [5]. Race disparity is also significant. Chinese are more sensitive to MS than Caucasian [2]. Finley et al. for the first time reported that a single-nucleotide polymorphism (SNP) in the α_2-adrenergic receptor gene correlated with individual differences in autonomic responsiveness to provocative motion and other stressors [26]. Recently, a genomewide association study conducted in 80,494 individuals from the 23 and Me database found that 35 SNPs in genes involved in balance function, eye, ear and cranial development, neurological processes, glucose homeostasis, or

hypoxia were associated with self-reported carsickness susceptibility [27]. Nevertheless, it has been verified that none of these SNPs is related to vestibular function regulation. It is noteworthy that some SNPs are in or near genes implicated in glucose and insulin homeostasis, which links to our pervious finding that hyperglycemia is related to the GI symptoms of MS both in human and rodents [28]. Recent studies have found that SNPs in genes of 5-Hydroxytryptamine type 3 receptor (5-HT_3), cholinergic muscarinic receptor type 3 (M3 AChR), morphine (μ) opioid receptor, and neurokinin 1 (NK_1) receptors are associated with background sensitivity to postoperative and chemotherapy-induced nausea and vomiting (PINV and CINV) [29]. These genetic bases for "final common pathway" of nausea and vomiting may also contribute to MS susceptibility.

Patients with migraine and Meniere's disease are prone to experience MS especially in female patients [30,31]. Mutations in genes related to vasculopathy and cortical spreading depression are responsible for vestibular symptoms and MS hypersusceptibility in migraine patients [32]. Previous studies have found sporadic Meniere's disease might be associated with mutations in genes of aquaporins and voltage-gated potassium channel expressed in the inner ear [33]. Given that these genes play important roles in endolymphatic homeostasis, their mutations ought to contribute to subnormal or asymmetrical otolith function associated with MS hypersusceptibility in Meniere patients.

Spaceflight and microgravity can affect the expression of genes associated with cellular functions [34,35]. Our study also showed that MS susceptible and insusceptible animals have different gene expression profile in the caudal VN after motion stimulation [36]. Moreover, for human T-lymphocyte cells, simulated microgravity exposure could alter the expression of genes involved in DNA methylation and histone modification, inducing DNA hypomethylation and mutational changes [37]. These lines of evidence indicate that epigenetic modulations might also contribute to MS susceptibility diversity and MS habituation. In addition, MS susceptibility is also influenced by personal characteristics including trait-anxiety, aerobic fitness, and hemodynamic as well as age and sex [38]. The linkage between genetic and epigenetic basis of these phenotypes and MS merits further investigation.

Prediction and Evaluation

Prevalence Prediction

It has been demonstrated that almost all healthy individuals can obtain MS when exposed to appropriate provocative motion. MS prevalence depends on individual threshold to motion stimulation and varies under different situations, which makes it difficult to predict. Lawther and Griffin established mathematical models with dependence on various vertical motion parameters (acceleration magnitude, frequency, and duration) for predicting incidence of seasickness [39]. Perez Arribas and Lopez Pinerio have proposed "sicken passengers ration" which represents variables including ship speed, loading condition, and sea state and includes the effect of passenger behavior and habituation to moving environment [40]. These formulas greatly improve ship design to increase the degree of comfort and the work ability on the sea.

Individual Susceptibility Prediction

Birren and Fisher for the first time provided a questionnaire approach to predict seasickness susceptibility [41]. Pensacola Motion History Questionnaire (PMHQ) and Reason and Brand MS Susceptibility Questionnaire (MSSQ) were nowadays commonly used in MS studies [42–44]. Golding redesigned a MSSQ-Short by simplifying the scoring and adding vital items including the demographic (e.g., age, gender, race), the nauseogenic environments avoidance (e.g., cars, planes, video games), and vestibular disorder comorbidities and anthropometric items (e.g., height, body weight, BMI) to increase the reliability and validity [45,46].

Shupac et al. and other groups assessed vestibular function, such as vestibular-ocular reflex (VOR), caloric stimulation, and vestibular-evoked myogenic potential (VEMP), to predict individual MS susceptibility [47–50]. Stoffregen et al. recently proposed the postural instability as a precursor of MS susceptibility [51]. Previous studies also demonstrated that computerized dynamic posturography (CDP) data can be used as indicator of seasickness susceptibility and habituation [52,53]. In addition, baseline protein concentration and amylase activity in saliva as well as odor and taster sensitivity were also used as indicators for predicting MS susceptibility in human subjects [54–57] (Table 1).

Diagnosis and Evaluation

MS can be diagnosed according to the manifestations during motion exposure after excluding other pathological disorders. Graybiel et al. and Wiker et al. established two MS severity grading criteria by scoring 7 categories of cardinal signs and symptoms, and 28 major, minor, or other symptoms, respectively [58,59]. Several research groups developed different questionnaires for assessing the multiple dimensions of MS symptoms [60–62] (Table 1).

Heart rate variability (HRV) and electrogastrogram (EGG) are useful for assessing cardiac sympathovagal interactions and gastric motility during MS, respectively [63,64]. HRV indices might be influenced by motion patterns, intersubject variations, subjects' self-adjustments, vomiting process, and stress response [65,66]. As for the EGG test, increased 4–9 cpm activity and the absence or decrease of 3 cpm activity may indicate MS-induced nausea and vomiting, respectively [64]. EGG has also been demonstrated to be more sensitive than electroencephalogram, electrocardiogram, and skin conductance in MS evaluation [67].

Fos protein, an indicator of neuronal activity, is considered to be a molecular indicator for MS development and habituation [68,69]. Nevertheless, whether Fos expression can illustrate race and sex difference in MS susceptibility is still unclear. Recently, we found that motion-induced elevation of serum glucose was significantly related to GI symptoms of MS and might serve as a potential MS marker [28] (Table 1).

Motion sickness Medications

In 1869, the first usage of medications for MS is a combination of chloroform and tincture of belladonna [70]. Nowadays, there are at least 9 different kinds of drugs used against MS. Anticholinergics and antihistamines are the most effective MS prophylactics with apparent side effects such as drowsiness and depression. Drug

Table 1 Prediction and evaluation for MS

Category	Description	Application	References
MS Questionnaires			
PMHQ	Coriolis stimulation, very low-frequency ship motion, and simulator stimulation as scoring keys	Predicting SS susceptibility	[42,44]
MSSQ	Childhood and adults history of transport or entertainment exposure and MS experience	Predicting susceptibility to real motion-induced MS	[43,45]
Graybiel rating scales	Rating cardinal symptoms including cold sweating, pallor, increases in salivation, drowsiness, headache, pain, and nausea and vomiting	Evaluating MS of all forms	[58]
Wiker rating scales	Rating MS by rigging up 28 major, minor, and other symptoms	Evaluating MS of all forms	[44,59]
Kennedy rating scales	Factor analysis of oculomotor, disorientation, and nausea dimensions	Evaluating SS	[60]
Muth rating scales	Rating 3 dimensions of nausea including gastrointestinal, somatic, and emotional distress	Assessing MS-induced nausea	[61]
Gianaros rating scales	Rating gastrointestinal, central, peripheral, and sopite-related dimensions	Multidimensional analysis of MS	[62]
Vestibular function			
VOR	Higher gains and lower phase leads	Predicting MS susceptibility; indicator of semicircular canal function	[47,48]
Caloric test	Faster slow-phase velocity	Predicting MS susceptibility; indicator of semicircular canal function	[165]
cVEMPs	Higher threshold; lower peak-to-peak amplitude interval	Predicting MS susceptibility; evaluating MS habituation; indicator of saccular function	[49,50]
Physiological indexes			
CDP	Less stability in condition 5 of SOT; decreased MCT strength	Predicting postural instability of MS susceptibles; evaluating MS habituation	[52,53]
Postural dynamics	Greater positional variability; higher temporal dynamics	Predicting postural instability of MS susceptibles	[51]
Odors and tastes sensitivity	Sensitive to unpleasant odors (e.g., petrol, leather); sensitive to phenylthiocarbamide tasters	Predicting susceptibility to environment incentives	[56,57]
HRV	Reduction in (HF) high-frequency component; increment in low-frequency component (LF) and LF/HF ratio	Evaluating MS-induced sympathovagal disturbance	[63,66]
EGG	Increased 4–9 cpm activity; absence or reduction of 3 cpm activity	Evaluating MS-induced gastric response	[50,64]
Core temperature	Reduction in core temperature	Evaluating MS-induced thermal reaction	[20]
Biochemical test			
Stress hormones	Increment in levels of AVP, ACTH, cortisol, beta-endorphin, etc. after provocative motion stimulation	Evaluating MS-induced stress	[23,166]
Salivary protein and amylase	High baseline salivary protein concentration; high amylase activity	Preceding MS susceptibility	[54,55]
Fos protein	Increase expression	Indicator of MS-related neuronal activation; evaluating vestibular habituation	[69,167]
Serum glucose	Elevated after provocative motion stimulation	Indicator of severity of GI symptoms of MS	[28]

SS, simulator sickness; SOT, sensory organization test; MCT, motor control test.

combinations are thus used to increase efficacy and alleviate side effects (Table 2).

Anticholinergics

Atropine, scopolamine (hyoscine), and hyoscyamine have already been used to treat MS before World War I. A recent cochrane systematic review of 14 randomized controlled trials (RCTs) concluded that scopolamine, the nonselective muscarinic cholinergic receptor (mAChR) antagonist, was more effective than placebo but not superior to antihistamines in preventing MS and was no more likely to induce drowsiness, blurring vision, or dizziness compared to other agents [71]. Nevertheless, the precise mAChR subtypes (M_1–M_5) that serve as the targets of scopolamine is still unclear. As we know that all mAChR subtypes are expressed in the brain, while only M_1, M_2, and M_5 exist in vestibular ganglia and vestibular end organs in humans [72]. The M_1, M_3, and M_5 are postsynaptic excitatory receptors; M_2 and M_4 receptors are inhibitory. Furthermore, selective M_3 and M_5 antagonist zamifenacin was found to be as effective as scopolamine in preventing

Table 2 Antimotion sickness medications

Category	Dosage formation	Usage	Application	References
Anticholinergics				
Scopolamine	p.o. (0.6 mg)	0.5–1 h before MS, effective within 6 h	Seasickness and experimental MS	[71]*
	TTS (1.5 mg/patch)	6–8 h before MS, effective over 72 h	Seasickness, airsickness, ship motion simulator, and experimental MS	[71]* [74,75]
	IN (0.4 mg)	0.5 h before MS, effective over 6 h	Experimental MS	[76,77]*
	p.o. (0.3 mg) + TTS	1 h before MS, effective over 72 h	Seasickness	[168]
Zamifenacin	p.o. (20 mg)	1.5 before MS	Experimental MS	[73]
Antihistamines				
Dimenhydrinate	p.o. (100 mg)	2 h before MS effective for 8 to 12 h	Seasickness and experimental MS	[84]* [169]
	CG (3 × 20 mg)	Chewed for 30 min each during MS	Experimental MS	[82]*
Cinnarizine	Oral (30 or 50 mg)	3 h before MS	Seasickness and flight simulator sickness	[170,171]
Cyclizine (Marezine)	p.o. (50 mg)	2 h before MS	Experimental MS	[172]
Promethazine	p.o. (25 or 50 mg)	2 h before MS, effective within 12 h	Space MS	[91,173]
	i.m. (25 or 50 mg)	1–2 h before MS, effective within 12 h	Space MS, parabolic flight and experimental MS	[92,174,175]
	Suppository (25 or 50 mg)	1–2 h before MS, effective within 12 h	Space MS	[175]
Meclizine (Antivert)	p.o. (25 or 50 mg)	1–2 h before MS, effective within 24 h	Experimental MS	[94,176]
Chlorpheniramine,	p.o. (4 or 12 mg)	3–4 h before MS	Experimental MS	[83]*
Betahistine	p.o. (32 or 48 mg)	1–2 h before MS	Seasickness and experimental MS	[89] [177]
Dopamine Antagonists				
Metoclopramide	i.v. (20 mg)	15 min after MS initiation	Carsickness	[97]*
5-$HT_{1B/1D}$ receptor agonist				
Rizatriptan	p.o. (10 mg)	2 h before MS	Experimental MS in migraineurs	[103]*
Sympathomimetics				
D-amphetamine	p.o. (10 mg)		Airsickness	[108]
Neuroleptics				
Phenytoin	p.o. (200 mg)	4 h before MS	Seasickness and parabolic flight MS	[117,118]
Baclofen	p.o. (20 mg)	0.5–1 h before MS	Experimental MS	[116]
Calcium channel blocker				
Flunarizine	–	–	Experimental MS	[125]†
μ-Opiate receptor agonist				
Loperamide	p.o. (16 mg)	3 h before MS	Experimental MS	[126]
Hormones				
Dexamethasone	i.v. (0.5 mg)	Every 6 h for 48 h	Experimental MS	[124]
Combination				
Promethazine + *d-amphetamine*	p.o. (25 mg+10 mg)	2 h before MS	Airsickness	[178]
Scopolamine + *d-amphetamine*	p.o. (0.4–1.2 mg+5 mg)	0.5–1 h before MS	Parabolic flight MS	[179]
Scopolamine + *ephedrine*	p.o. (0.3 mg+25 mg)	0.5–1 h before MS or 3 times daily	Seasickness and experimental MS	[180]*
	i.m. (0.2 mg+25 mg)	30 min before MS	Experimental MS	[181]
Chlorpheniramine + *ephedrine*	p.o. (12 mg+50 mg)	3–4 h MS	Experimental MS	[83]*
Dimenhydrinate + scopolamine	–	–	Air sickness	[182]†

p.o., per os; TTS, transdermal therapeutic system; IN, intranasal; CG, chewing gum; i.m., intramuscular; i.v., intravenous. *Randomized control trials. †Dosage unavailable.

MS [73]. These lines of evidence suggest that scopolamine might exert its antagonistic effect on peripheral M_1 and M_5 and/or central M_1 and M_3 mAChR to prevent MS.

The commonly used dosage forms of scopolamine include oral tablets and liquid, transdermal therapeutic system (TTS), and the intranasal (IN) aerosol (Table 2). The TTS delivering scopolamine to the mastoid area shows a long-lasting prophylactic effect without psychomotor impairment [74,75]. Noninvasive IN formulation of scopolamine has higher peak plasma concentration and shorter peak time than oral agents [76,77]. In addition, grapefruit

juice can increase the bioavailability of orally administrated scopolamine via inhibiting the cytochrome P-450 3A enzymes which are involved in oxidative demethylation of the scopolamine, while the efficacy of IN and TTS of scopolamine are affected by pH value [78,79].

Antihistamines

In 1949, Gray and Carliner for the first time discovered that antihistamine dimenhydrinate was effective in preventing seasickness [80]. Small RCTs have verified the effectiveness of the first-generation H_1 antihistamines against MS, but the second generations were ineffective [81–84] (Table 2). Physiological studies suggested that dimenhydrinate, cinnarizine, and meclizine exerted a central action on the medial VN in which high density of H_1 and H_2 receptor were present [85,86], while the promethazine had global suppression effect on vestibular system, but all these antihistamines had no effect on the central autonomic regions [87]. Betahistine, an H_3 receptor antagonist and a weak H_1 receptor agonist, is effective in the preventing seasickness and increases tolerability to Coriolis accelerations via reducing histamine release in medial VN [88,89]. Recent studies found that H_4 receptors were expressed in rat vestibular ganglia, and H_4 receptor antagonists had a pronounced inhibitory effect on primary vestibular neuron activity and significantly alleviated vestibular deficits in rats [90]. These results highlighted H_4 receptors as potential pharmacological targets for treating MS.

The main dosage forms of antihistamines include oral (all), intramuscular injection (promethazine and cyclizine), suppository (promethazine), chewing gum (dimenhydrinate), and sublingual form (dimenhydrinate) [91]. Putcha et al. found that promethazine, as the only drug given by three different routes (orally, intramuscularly, and rectally), was most effective and had minimal side effects when administered intramuscularly in astronauts during space shuttle missions [92]. The diphenhydramine chewing gum has been developed to alleviate antihistamine's adverse effects [82,93]. Recently, a new suspension formulation of meclizine was developed with a more rapid effect and higher maximum concentration than marketed oral tablet [94].

Monoamine Antagonists/Agonist

Dopamine D_2 and D_3 receptors are known to play a role in nausea and emesis. They can alter the amount of cAMP within neurons of the vomiting center via inhibiting adenylate cyclase [95]. Competitive D_2 receptor antagonist metoclopramide, administered through intravenous or intramuscular injection but not oral route, alleviated overall symptoms and restored gastric emptying after the initiation of MS [96,97]. In addition, orally administered domperidone, a peripherally restricted D_2 receptor antagonist and α_1-adrenoceptor antagonist, failed to prevent spatial disorientation-induced gastric dysrhythmia and MS symptoms in humans [98,99] (Table 2). These results suggest that effectiveness of dopamine antagonists may depend on the administration route and timing. Similarly, although the 5-HT_3 receptor antagonists ondansetron are extensively used to prevent and suppress CINV and PONV [100], oral administration of this drug has no preventive effect against seasickness or experimental MS [101,102]. As MS can induce delayed gastric emptying and reduce absorption, oral forms are problematic and injection or transdermal formation is recommended.

Additionally, two double-blind, placebo-controlled studies showed that 5-$HT_{1B/1D}$ receptor agonist rizatriptan prevented the development of MS in migrainous patients [103,104]. The 5-HT_{2A} antagonist ketanserin significantly suppressed hypergravity-induced hypophagia in rats, while a 5-HT_{1A} agonist, 8-hydroxy-2-(di-n-propylamino) tetralin hydrobromide (8-OH-DPAT), successfully prevented vomiting induced by motion in cats and suncus murinus [105–107]. The precise efficacy of these drugs against MS in humans needs to be verified in the future.

Stimulants and Sedatives

Sympathomimetics d-amphetamine was found to be highly effective against space MS rather than seasickness [108]. Accumulating evidence suggests that d-amphetamine and ephedrine might counteract the sedative side effects of scopolamine and antihistamines, but at the risk of drug addiction and counterbalancing the vestibular suppression effect (Table 2). Nevertheless, scopolamine used in combination with d-amphetamine against MS should be cautioned, for scopolamine impairs decision-making and motivational behavior similar to the effect produced by amphetamine [109]. Modafinil, a potential substitute of amphetamine, significantly enhanced the efficacy of scopolamine when used in combination in rodents [110], but failed to prevent MS in humans when used alone [111]. Caffeine, a much more commonly used psychostimulant, was found to be effective in counteracting scopolamine-induced memory impairment in humans and animals [112,113], while no study has been performed to evaluate efficacy of caffeine in the management of MS alone or in combination with scopolamine and antihistamines. Neuroleptics including barbiturates, diazepam, and baclofen as well as phenytoin were found to be effective in prevention of MS [114–118] (Table 2).

Other Drugs

Clinical studies have demonstrated that powdered ginger was as effective as other anti-emetics in reducing the incidence of nausea and vomiting caused by traveling, while exploratory experimental studies had controversial outcomes possibly due to different stimulation patterns and evaluation methods used [119,120]. Chinese medicinal compound recipe composed of ginger, pogostemonis herba, and radix aucklandiae and an ancient prescription Pingandan are also found to be effective against MS in animals [121,122]. Our study revealed that ginsenosides combined with dexamethasone can significantly increase tolerance to acceleration in rats [123], consisting with early findings that dexamethasone can reduce susceptibility to space MS in humans [124] (Table 2). Flunarizine, a calcium channel blocker, was shown to be a peripherally acting labyrinthine suppressant. It was effective in preventing MS without central depressive side effects [125]. A placebo-controlled, crossover study showed that the peripheral acting μ-opiate agonist loperamide attenuated vertical axis rotation-induced nausea in humans [126]. The NK_1 receptor antagonist aprepitant is successfully used for preventing acute and delayed CINV [127]. The NK_1 receptor antagonists are also effec-

tive against MS-induced emesis in animals but not in humans [128–130]. Recent findings have demonstrated that MS is associated with impaired endocannabinoid activity [123,131,132]. CB1 receptor agonist (Δ9-tetrahydrocannabinol, Δ9-THC) and antagonist (cannabidiolic acid) were observed to inhibit emesis induced by motion in suncus murinus via different neural mechanism [133,134].

Nonpharmacological Countermeasures

Habituation Training

Transient MS habituation can be induced in animals and humans by repeated or prolonged motion stimulation and may generally last for several weeks [69,135,136]. The habituation acquired under particular stimulus conditions is normally highly specific, while the time-course of habituation acquirement for linear acceleration is quite different from that for angular acceleration in humans [137]. Repeated exposure may produce more sufficient habituation than single prolonged stimulation, but desensitization to one provocative motion could not be transferred to a more severe motion stimulus [138]. Thus, the objective of habituation training is to reproduce the sensory conflict as close as possible to the provocative environment. For instance, horizontal suspension, parabolic flight, and neutral buoyancy simulation have been used as microgravity simulation methods for astronaut training [139,140]. Recent studies have demonstrated that preflight virtual reality training is also effective against space MS and disorientation [141]. As sufficient activation of vestibular system is the prerequisite to produce novel "internal model," anti-MS drugs are not recommended during MS habituation training process [137,142].

Compared with conventional ground-based training procedures using revolving chair, winding stair, idler wheel, and swing, combined visual-vestibular habituation training was more effective and can produce long-term effect against travel-induced MS for up to 18 weeks in susceptible subjects [143,144]. Recent prospective studies also showed that optokinetic training comprising vertical, horizontal, and torsional movements of frontly projected bright spots can reconstitute the effects of swell encountered at sea and appears to be an effective training modality for the prevention of disabling seasickness [145]. In addition, the pseudorandom galvanic vestibular stimulation (GVS) is expected to be used in astronaut training against landing sickness, as it accurately replicated the postural instability, locomotor impairment, and reduced dynamic visual acuity observed in astronauts after return from space [146].

Behavioral and other Countermeasures

Forward-looking vision on the distant horizon is effective in alleviating MS symptoms via matching visual and vestibular information in subjects exposed to simulated ship motion [147]. Controlled breathing is also beneficial for managing MS symptoms and promoting habituation [148,149]. Nevertheless, breathing supplemental oxygen had no advantage over breathing air in reducing MS in healthy adults [150]. MS symptoms can be alleviated by autogenic-feedback training exercise for autonomic responses control as well as the manipulations to enhance predictability and positive expectancy [151–153]. Recently, smoking deprivation, pleasant music, and odors as well as head vibration and mental distraction have been found to be effective in reducing MS symptoms [154–157].

High sodium and energy dense or low vitamin A, vitamin C, and iron diets as well as high frequency of meals in previous 24 h increased the airsickness occurrences in pilots [158]. A protein-predominant beverage taken 5 or 30 min before optokinetic stimulation was found to be effective in suppressing gastric tachyarrhythmia and MS symptoms [159]. A recent double-blind, placebo-controlled crossover study found that vitamin C was effective in suppressing symptoms of seasickness, particularly in youngsters [160].

Acupuncture at the P6 or Neiguan point to treat nausea and vomiting has been practiced in China for many years, but it is still controversial whether SeaBand or ReliefBand designed for acupressure or electrostimulation at P6 are effective in MS treatment [161,162]. Transcutaneous electrical nerve stimulation of the posterior neck and the right Zusanli acupoint was found to be effective in reducing simulator sickness symptoms and alleviating cognitive impairment [163]. Recently, stroboscopic illumination at 8 herts, by ambient strobe light or by liquid crystal display shutter glasses, reduced the severity of MS symptoms and improved the performance on the vigilance task in soldiers exposed to a nauseogenic flight in a helicopter [164].

Conclusion

This study reviews the progress of sensory conflict theory, vestibular homeostasis regulation and genetic basis of MS. It also summarizes prediction and evaluation, and available countermeasures. In sensory conflict theory, the "sensory conflict neurons" remain activated and ultimately disrupt homeostasis and trigger MS responses if the provocative motion signal or reafference information mismatches the "internal model." The heredity of MS susceptibility involves genetic and epigenetic regulation on genes participating in cellular metabolism, autonomic regulation, and vestibular function and development. Several methods are used for MS prediction and evaluation, but specific indicator is scarce. The efficacy of anti-MS medications depends on dosage forms and time of administration. Novel drugs in development show no remarkable advantages over traditional medications such as anticholinergics and antihistamines. Visual-vestibular habituation training is the most effective nonpharmacological prophylaxis. Other measures such as acupuncture and stroboscopic illumination could be substitutes for medications when side effects are unacceptable.

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Conflict of Interest

The authors declare no conflict of interest.

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